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(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; P.O. Box 2000, 126 East Lincoln Avenue, RY 6030, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **COSFORD, Nicholas, D., P.** [GB/US]; 7161 Rock Valley Court, San Diego, CA 92122 (US). **MCDONALD, Ian, A.** [AU/US]; 4722 Shadwell Place, San Diego, CA 92130 (US). **BLEICHER, Leo, Solomon** [US/US]; 555 Rushville Street, La Jolla, CA 92037 (US). **CUBE, Rowena, V.** [US/US]; 3667 Caminito Cielo Del Mar, San Diego, CA 92130 (US). **SCHWEIGER, Edwin, J.** [US/US]; 11286 Caminito Aclara, San Diego, CA 92126-6101 (US). **VERNIER, Jean-Michel** [FR/US]; 7161 Rock Valley Court, San Diego, CA 92122 (US). **HESS, Stephen, D.** [US/US]; 9466 Vervain Street, San Diego, CA 92129 (US). **VARNEY, Mark, A.** [GB/US]; 13202 Thunderhead Street, San Diego, CA 92129 (US). **MUNOZ, Benito** [CA/US]; 10741 Frank Daniels Way, San Diego, CA 92131 (US).

(74) Agent: **REITER, Stephen, E.**; Gray Cary Ware & Freidenrich, LLP, Suite 1600, 4365 Executive Drive, San Diego, CA 92121-2189 (US).

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(54) Title: HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF

(57) Abstract: In accordance with the present invention, there are provided novel class of heterocyclic compounds and methods of use thereof. Compounds of the invention contain a substituted, unsaturated five, six or seven membered heterocyclic ring that includes at least one nitrogen atom and at least one carbon atom. At a ring position adjacent to a ring nitrogen atom, the heterocyclic ring has at least one substituent which includes a moiety, linked to the heterocyclic ring via an alkylene moiety, an alkynylene moiety or an azo group. Invention compounds are capable of a wide variety of uses including modulating physiological processes by functioning as agonists and antagonists of receptors in the nervous system, as insecticides, and as fungicides. The invention further provides methods of modulating the activity of excitatory amino acid receptors using a specifically defined class of heterocyclic compounds including the novel compounds referred to above. In one embodiment, there are provided methods of modulating metabotropic glutamate receptors. The present invention also discloses methods of treating disease using heterocyclic compounds. The invention further discloses methods of preventing disease conditions related to diseases of the pulmonary system, diseases of the nervous system, diseases of the cardiovascular system, diseases of the gastrointestinal system, diseases of the endocrine system, diseases of the exocrine system, diseases of the skin, cancer and diseases of the ophthalmic system. The invention also discloses pharmaceutically acceptable salt forms of the above-described heterocyclic compounds.

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HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF

FIELD OF INVENTION

The present invention relates to novel heterocyclic compounds which contain a heterocylic ring bearing at least one substituent attached by a linker containing an acetylenic group, a vinylic group or an azo group. In addition, the present invention relates to therapeutic methods of use of heterocyclic compounds for the treatment and prevention of various disease conditions.

BACKGROUND OF THE INVENTION

Unsaturated heterocylic compounds find a wide variety of uses. For example, compounds of this class find uses as modulators of physiological processes that are mediated by ligand-activated receptors. Receptors that are activated by ligands are located throughout the nervous, cardiac, renal, digestive and bronchial systems, among others. Therefore, in the nervous system, for example, heterocyclic compounds are capable of functioning as agonists or antagonists of receptors for neurotransmitters, neurohormones and neuromodulators. Ligand-activated receptors have been identified in a wide variety of species, including humans, other mammals and vertebrates as well as in invertebrate species. Therefore, compounds of this class are also able to modulate receptor-mediated processes throughout phylogeny and find uses in a wide variety of applications, *e.g.*, as pharmaceuticals, insecticides and fungicides.

Receptors activated by excitatory amino acids, such as the amino acid L-glutamic acid (glutamate), are a major excitatory neurotransmitter receptor class in the mammalian central nervous system. Anatomical, biochemical and electrophysiological analyses suggest that glutamatergic systems are involved in a broad array of neuronal processes, including fast excitatory synaptic transmission, regulation of neurotransmitter release, long-term potentiation, long-term depression, learning and memory, developmental synaptic plasticity, hypoxic-ischemic damage and neuronal cell death, epileptiform seizures, visual processing, as well as the pathogenesis of several neurodegenerative disorders. See generally, Nakanishi *et al., Brain Research Reviews* 26:230-235 (1998); Monaghan *et al., Ann. Rev. Pharmacol. Toxicol.* 29:365-402 (1980). This extensive repertoire of functions, especially those related to learning, neurotoxicity, and neuropathology, has stimulated recent attempts to describe and define the mechanisms through which glutamate exerts its effects.

Glutamate has been observed to mediate its effects through receptors that have been categorized into two main groups: ionotropic and metabotropic. Metabotropic glutamate receptors are divided into three groups based on amino acid sequence homology, transduction mechanism and pharmacological properties, namely Group I, Group II and Group III. Each Group of receptors contains one or more types of receptors. For example, Group I includes metabotropic glutamate receptors 1 and 5 (mGluR1

and mGluR5), Group II includes metabotropic glutamate receptors 2 and 3 (mGluR2 and mGluR3) and Group III includes metabotropic glutamate receptors 4, 6, 7 and 8 (mGluR4, mGluR6, mGluR7 and mGluR8). Several subtypes of a mGluR type may exist. For example, subtypes of mGluR1 include mGluR1a, mGluR1b, mGluR1c and mGluR1d.

Anatomical studies demonstrate a broad and selective distribution of metabotropic glutamate receptors in the mammalian nervous system. For example, mGluR1 is expressed in the cerebellum, olfactory bulb, hippocampus, lateral septum, thalamus, globus pallidus, entopeduncular nucleus, ventral pallidum and substantia nigra (Petralia *et al.*, (1997) *J. Chem. Neuroanat.*, 13:77-93; Shigemoto *et al.*, (1992) *J. Comp. Neurol.*, 322:121-135). In contrast, mGluR5 is weakly expressed in the cerebellum, while higher levels of expression are found in the striatum and cortex (Romano *et al.*, (1995) *J. Comp. Neurol.*, 355:455-469). In the hippocampus, mGluR5 appears widely distributed and is diffusely expressed.

Metabotropic glutamate receptors are typically characterized by seven putative transmembrane domains, preceded by a large putative extracellular amino-terminal domain and followed by a large putative intracelluar carboxy-terminal domain. The receptors couple to G-proteins and activate certain second messengers depending on the receptor group. Thus, for example, Group I mGluRs activate phospholipase C. Activation of the receptors results in the hydrolysis of membrane phosphatidylinositol (4,5)-bisphosphate to diacylglycerol, which activates protein kinase C, and inositol trisphosphate, which in turn activates the inositol trisphosphate receptor to promote the release of intracellular calcium.

Ionotropic glutamate receptors are generally divided into two classes: the *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors. Both classes of receptors are linked to integral cation channels and share some amino acid sequence homology. GluR1-4 are termed AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors because AMPA preferentially activates receptors composed of these subunits, while GluR5-7 and KA1-2 are termed kainate receptors as these are preferentially sensitive to kainic acid. Thus, an "AMPA receptor" is a non-NMDA receptor that can be activated by AMPA. AMPA receptors include the GluR1-4 family, which form homo-oligomeric and hetero-oligomeric complexes which display different current-voltage relations and calcium permeability. Polypeptides encoded by GluR1-4 nucleic acid sequences can form functional ligand-gated ion channels. An AMPA receptor includes a receptor having a GluR1, GluR2, GluR3 and/or GluR4 subunit. A NMDA receptor includes a receptor having NMDAR1, NMDAR2a, NMDAR2b, NMDAR2c, NMDAR2d and/or NMDAR3 subunits.

Because of the physiological and pathological significance of excitatory amino acid receptors generally and metabotropic glutamate receptors, in particular, there is a need to identify methods of

modulating excitatory amino acid receptor-mediated processes, as well as therapeutic methods of treatment and methods for prevention of diseases. Also, there is a continuing need in the art for new members of a compound class that can modulate excitatory amino acid receptors. The present invention satisfies these and related needs.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel class of heterocyclic compounds. Compounds of the invention contain a substituted, unsaturated five-, six- or seven-membered heterocyclic ring that includes at least one nitrogen atom and at least one carbon atom. The ring additionally includes three, four or five atoms independently selected from carbon, nitrogen, sulfur and oxygen atoms. The heterocyclic ring has at least one substituent located at a ring position adjacent to a ring nitrogen atom. This mandatory substituent of the ring includes a moiety (B), linked to the heterocyclic ring via a hydrocarbyl or an azo group. The invention also discloses pharmaceutically acceptable salt forms of heterocyclic compounds.

Invention compounds are useful for a wide variety of applications. For example heterocyclic compounds can act to modulate physiological processes by functioning as agonists and antagonists of receptors in the nervous system. Invention compounds may also act as insecticides and as fungicides. Pharmaceutical compositions containing invention compounds also have wide utility.

In accordance with the present invention, there are also provided methods of modulating the activity of excitatory amino acid receptors using a specifically defined class of heterocyclic compounds. In one embodiment, there are provided methods of modulating metabotropic glutamate receptors. The present invention also provides methods of treating disease using heterocyclic compounds. Diseases contemplated include cerebral ischemia, chronic neurodegeneration, psychiatric disorders, schizophrenia, mood disorders, emotion disorders, disorders of extrapyramidal motor function, obesity, disorders of respiration, motor control and function, attention deficit disorders, concentration disorders, pain disorders, neurodegenerative disorders, epilepsy, convulsive disorders, eating disorders, sleep disorders, sexual disorders, circadian disorders, drug withdrawal, drug addiction, compulsive disorders, anxiety, panic disorders, depressive disorders, skin disorders, retinal ischemia, retinal degeneration, glaucoma, disorders associated with organ transplantation, asthma, ischemia and astrocytomas. The invention further discloses methods of preventing disease conditions related to diseases of the pulmonary system, diseases of the nervous system, diseases of the cardiovascular system, diseases of the gastrointestinal system, diseases of the endocrine system, diseases of the exocrine system, diseases of the skin, cancer and diseases of the ophthalmic system.

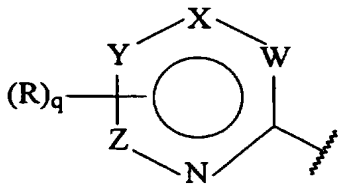
DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided compounds having the structure:

A — L — B

or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, wherein:

A is a 5-, 6- or 7-membered ring having the structure:



wherein at least one of W, X, Y and Z is (CR)p, wherein p is 0, 1 or 2;

the remainder of W, X, Y and Z are each independently O, N or S; and

each R is independently halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide, wherein q is 0, 1, 2 or 3;

L is substituted or unsubstituted alkenylene, alkynylene, or azo; and

B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, or substituted or unsubstituted aryl;

provided, that the following compounds are excluded:

the compounds wherein **A** is a 6-membered ring wherein:

W, X, Y and **Z** are $(CR)_p$ wherein p is 1; and

R at the W position is hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, unsubstituted or hydroxy-substituted lower alkyleneamino-lower alkyl, lower alkoxy, lower alkanoyloxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, phthalimido-lower alkoxy, unsubstituted or hydroxy- or 2-oxo-imidazolidin-1-yl-substitued lower alkyleneamino-lower alkoxy, carboxy, esterified or amidated carboxy, carboxy-lower alkoxy or esterified carboxy-lower-alkoxy; R at the X position is hydrogen; R at the Y position is hydrogen, lower alkyl, carboxy, esterified carboxy, amidated carboxy, hydroxy-lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy; and R at the Z position is hydrogen, lower alkyl, hydroxy-lower alkyl, carboxy, esterified carboxy, amidated carboxy, unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-lower alkyl-N-phenylcarbamoyl, lower alkoxy, halo-lower alkyl or halo-lower alkoxy;

L is substituted or unsubstituted alkenylene, alkynylene or azo,

B is substituted or unsubstituted aryl or heterocycle having two or more double bonds, wherein substituents are independently lower alkyl, lower alkenyl, lower alkynyl, phenyl, phenyl-lower alkynyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo and halo-lower alkyl, wherein phenyl, phenyl-lower alkynyl, phenoxy, and phenyl-lower alkoxy may bear further substituents; and

the compounds wherein **A** is a 6-membered ring wherein:

W, X, Y and **Z** are $(CR)_p$ wherein p is 1; R at the X position is not hydrogen; and R at the W, Y and Z positions are hydrogen;

L is alkenylene or alkynylene; and

B is a substituted or unsubstituted aryl or heterocycle containing two or more double bonds; and

the compounds wherein **A** is a 5-membered ring wherein:

one of **W, X, Y** and **Z** is $(CR)_p$, and p is 0, two of **W, X, Y** and **Z** are $(CR)_p$ and p is 1, and the remaining variable ring member is O or S; or

one of **W, X, Y** and **Z** is N, one of **W, X, Y** and **Z** is $(CR)_p$ and p is 1, one of **W, X, Y** and **Z** is $(CR)_p$ and p is 0, and the remaining variable ring member is O, S or $(CR)_p$, and p is 1; or

two of **W, X, Y** and **Z** are N, one of **W, X, Y** and **Z** is $(CR)_p$, and p is 0, and the remaining variable ring member is , O or S or $(CR)_p$, and p is 1;

each R is independently hydrogen, nitro, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, C_1-C_4-haloalkylthio, C_3-C_6-alkenyl or C_3-C_8-cycloalkyl;

L is alkynylene; and

B is substituted or unsubstituted aryl, wherein substituents are independently nitro, cyano, C_1-C_6-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkthio, C_1-C_4-haloalkylthio, C_1-C_4-alkoxycarbonyl, C_3-C_6-alkenyl, phenyl or phenoxy, wherein phenyl and phenoxy may bear further substituents; and

the compounds wherein **A** is a 6-membered ring wherein:

W, X, Y and **Z** are (CR)p, wherein p is 1 and R is hydrogen,

L is alkynylene; and

B is unsubstituted 1-cyclopenten-1-yl or unsubstituted 1-cyclohexen-1-yl; and

the compounds wherein **A** is a 5-membered ring wherein:

W is (CR)p, and p is 0, **Y and Z** are (CR)p, and p is 1, **X** is N or S; and R is phenyl; or

W is (CR)p, and p is 0, **X and Z** are (CR)p, and p is 1, **Y** is O, N or S; and R is phenyl;

L is unsubstituted alkenylene and

B is unsubstituted phenyl; and

the compounds wherein **A** is a 5-membered ring containing two double bonds, wherein one of **W, X, Y** and **Z** is $(CR)_p$, and p is 0, and the remaining ring members are $(CR)_p$ and p is 1; and

the compounds wherein **A** is unsubstituted heterocycle containing two or more double bonds; **L** is alkenylene or alkynylene, and **B** is unsubstituted phenyl.

As employed herein, "hydrocarbyl" refers to straight or branched chain univalent and bivalent radicals derived from saturated or unsaturated moieties containing only carbon and hydrogen atoms, and having in the range of about 1 up to 12 carbon atoms. Exemplary hydrocarbyl moieties include alkyl moieties, alkenyl moieties, dialkenyl moieties, trialkenyl moieties, alkynyl moieties, alkadiynal moieties, alkatriynal moieties, alkenyne moieties, alkadienyne moieties, alkenediyne moieties, and the like. The term "substituted hydrocarbyl" refers to hydrocarbyl moieties further bearing substituents as set forth below.

As employed herein, "alkyl" refers to straight or branched chain alkyl radicals having in the range of about 1 up to 12 carbon atoms; "substituted alkyl" refers to alkyl radicals further bearing one or more substituents such as hydroxy, alkoxy, mercapto, aryl, heterocycle, halogen, trifluoromethyl, pentafluoroethyl, cyano, cyanomethyl, nitro, amino, amide, amidine, amido, carboxyl, carboxamide, carbamate, ester, sulfonyl, sulfonamide, and the like.

As employed herein, "alkenyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 6 carbon atoms presently preferred), and "substituted alkenyl" refers to alkenyl radicals further bearing one or more substituents as set forth above.

As employed herein, "alkenylene" refers to straight or branched chain divalent alkenyl moieties having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms (with divalent alkenyl moieties having in the range of about 2 up to 6 carbon atoms presently preferred), and "substituted lower alkenylene" refers to divalent alkenyl radicals further bearing one or more substituents as set forth above.

As employed herein, "alkynyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 6 carbon atoms presently being preferred), and "substituted alkynyl" refers to alkynyl radicals further bearing one or more substituents as set forth above.

As employed herein, "alkynylene" refers to straight or branched chain divalent alkynyl moieties having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with divalent alkynyl moieties having two carbon atoms presently being preferred), and "substituted alkynylene" refers to divalent alkynyl radicals further bearing one or more substituents as set forth above.

As employed herein, "cyclohydrocarbyl" refers to cyclic (*i.e.*, ring-containing) univalent radicals derived from saturated or unsaturated moieties containing only carbon and hydrogen atoms, and having in the range of about 3 up to 20 carbon atoms. Exemplary cyclohydrocarbyl moieties include cycloalkyl moieties, cycloalkenyl moieties, cycloalkadienyl moieties, cycloalkatrienyl moieties, cycloalkynyl moieties, cycloalkadiynyl moieties, spiro hydrocarbon moieties wherein two rings are joined by a single atom which is the only common member of the two rings (*e.g.*, spiro[3.4]octanyl, and the like), bicyclic hydrocarbon moieties wherein two rings are joined and have two atoms in common (*e.g.*, bicyclo [3.2.1]octane, bicyclo [2.2.1]hept-2-ene, norbornene, decalin, and the like), and the like. The term "substituted cyclohydrocarbyl" refers to cyclohydrocarbyl moieties further bearing one or more substituents as set forth above.

As employed herein, "cycloalkyl" refers to ring-containing alkyl radicals containing in the range of about 3 up to 20 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl radicals further bearing one or more substituents as set forth above.

As employed herein, "cycloalkenyl" refers to ring-containing alkenyl radicals having at least one carbon-carbon double bond in the ring, and having in the range of about 3 up to 20 carbon atoms, and "substituted cycloalkenyl" refers to cyclic alkenyl radicals further bearing one or more substituents as set forth above.

As employed herein, "cycloalkynyl" refers to ring-containing alkynyl radicals having at least one carbon-carbon triple bond in the ring, and having in the range of about 3 up to 20 carbon atoms, and "substituted cycloalkynyl" refers to cyclic alkynyl radicals further bearing one or more substituents as set forth above.

As employed herein, "aryl" refers to mononuclear and polynuclear aromatic radicals having in the range of 6 up to 14 carbon atoms, and "substituted aryl" refers to aryl radicals further bearing one or more substituents as set forth above, for example, alkylaryl moieties.

As employed herein, "heterocycle" refers to ring-containing radicals having one or more heteroatoms (*e.g.*, N, O, S) as part of the ring structure, and having in the range of 3 up to 20 atoms in the ring. Heterocyclic moieties may be saturated or unsaturated when optionally containing one or more double bonds, and may contain more than one ring. Heterocyclic moieties include, for example, monocyclic moieties such as imidazolyl moieties, pyrimidinyl moieties, isothiazolyl moieties, isoxazolyl moieties, moieties, and the like, and bicyclic heterocyclic moieties such as azabicycloalkanyl moieties, oxabicycloalkyl moieties, and the like. The term "substituted heterocycle" refers to heterocycles further bearing one or more substituents as set forth above.

As employed herein, "azo" refers to the bivalent moiety –N=N–, wherein each single bond is attached to a different carbon atom.

As employed herein, "halogen" refers to fluoride, chloride, bromide or iodide radicals.

In accordance with the present invention, A is a 5-, 6- or 7-membered unsaturated heterocyclic moiety, containing a ring having at least one nitrogen atom located on the ring in a position adjacent to a carbon atom which bears a linking moiety as a substituent. The ring further contains 3, 4 or 5 independently variable atoms selected from carbon, nitrogen, sulfur and oxygen. Thus, A can be pyridinyl, imidazolyl, pyridazinyl, pyrimidinyl, pyrazoyl, pyrazinyl, triazolyl, triazinyl, tetrazolyl, tetrazinyl, isoxazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, oxadiazinyl, isothiazolyl, thiazoyl, dioxazolyl, oxathiazolyl, oxathiazinyl, azepinyl, diazepinyl, and the like. Those of skill in the art will recognize that multiple isomers exist for a single chemical formula; each of the possible isomeric forms of the various empirical formulae set forth herein are contemplated by the invention. When a variable ring atom is carbon, it bears a hydrogen, or is optionally substituted with halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, thiol, nitro, carboxyl, ester, cyano, amine, amide, carboxamide, amidine, amido, sulfonamide, and the like, with presently preferred embodiments having no substituent (*i.e.*, q is 0) or bearing the following substituents: halogen, alkyl, containing one up to four carbon atoms, fluorinated alkyl, containing one up to four carbon atoms, aryl, and amine. Substitution at position Z of the ring is presently preferred.

In accordance with one embodiment of the invention, A is a 5-, 6- or 7-membered ring containing, as ring members, a nitrogen atom and a sulfur atom. Moieties contemplated for use by this embodiment of the invention include those wherein A is isothiazol-3-yl (1,2-thiazol-3-yl), thiazol-4-yl (1,3,-thiazol-4-yl), thiazol-2-yl (1,3-thiazol-2-yl), 1,2-thiazin-3-yl, 1,3-thiazin-4-yl, 1,4-thiazin-3-yl, 1,3-thiazin-2-yl, thiazepinyl, and the like. Presently preferred moieties include those wherein A is isothiazol-3-yl (1,2-thiazol-3-yl), thiazol-4-yl (1,3-thiazol-4-yl) and thiazol-2-yl (1,3-thiazol-2-yl).

In accordance with another embodiment of the invention, A is a 5-, 6- or 7-membered ring containing, as ring members, a nitrogen atom and an oxygen atom. Moieties contemplated by this

embodiment of the invention include those wherein A is 1,2-oxazin-3-yl, 1,3-oxazin-4-yl, 1,4-oxazin-3-yl, 1,3-oxazin-2-yl, oxazol-2-yl, isoxazol-3-yl, oxazol-4-yl, oxazepinyl, and the like. Presently preferred moieties include those wherein A is oxazol-2-yl, isoxazol-3-yl and oxazol-4-yl.

In accordance with another embodiment of the invention, A is a 5-, 6- or 7-membered ring containing, as a ring member, a nitrogen atom. Moieties contemplated by this embodiment of the invention include those wherein A is 2-pyridinyl and 2-pyrrolyl.

In accordance with another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing, as ring members, two nitrogen atoms. Moieties contemplated by this embodiment of the invention include those wherein A is 3-pyridazinyl (1,2-diazin-3-yl), pyrimidin-4-yl (1,3-diazin-4-yl), pyrazin-3-yl (1,4-diazin-3-yl), pyrimidin-2-yl (1,3-diazin-2-yl), pyrazol-3-yl (1,2-diazol-3-yl), imidazol-4-yl (1,3-isodiazol-4-yl, imidazol-2-yl (1,3-isodiazol-2-yl), diazepinyl, and the like. Presently preferred moieties include those wherein A is 3-pyridazinyl (1,2-diazin-3-yl), pyrimidin-4-yl (1,3-diazin-4-yl), pyrazin-3-yl (1,4-diazin-3-yl), pyrimidin-2-yl (1,3-diazin-2-yl), 1,3-isodiazol-4-yl and 1,3-isodiazol-2-yl.

In accordance with still another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing, as ring members, three nitrogen atoms. Moieties contemplated by this embodiment of the invention include those wherein A is 1,2,3-triazin-4-yl, 1,2,4-triazin-6-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,3,5-triazin-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl, triazepinyl, and the like. Presently preferred moieties include those wherein A is 1,2,3-triazin-4-yl, 1,2,4-triazin-6-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,3,5-triazin-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl.

In accordance with still another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing, as ring members, four nitrogen atoms. Moieties contemplated for use in the practice of the invention include those wherein A is tetrazin-2-yl, tetrazin-3-yl, tetrazin-5-yl, tetrazolyl, tetrazepinyl, and the like. Presently preferred moieties include those wherein A is tetrazolyl.

In accordance with yet another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing, as ring members, one sulfur atom and two nitrogen atoms. Moieties contemplated by this embodiment of the invention include those wherein A is 1,2,6-thiadiazin-3-yl, 1,2,5-thiadiazin-3-yl, 1,2,4-thiadiazin-3-yl, 1,2,5-thiadiazin-4-yl, 1,2,3-thiadiazin-4-yl, 1,3,4-thiadiazin-5-yl, 1,3,4-thiadiazin-2-yl, 1,2,4-thiadiazin-5-yl, 1,3,5-thiadiazin-4-yl, 1,3,5-thiadiazin-2-yl, 1,2,4-thiadiazol-3-yl, 1,2,3-thiadiazol-4-yl, 1,3,4-thiadiazol-2-yl, 1,2,5-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, thiadiazepinyl, and the like. Presently preferred moieties include those wherein A is 1,2,4-thiadiazol-3-yl, 1,2,3-thiadiazol-4-yl, 1,3,4-thiadiazol-2-yl, 1,2,5-thiadiazol-3-yl and 1,2,4-thiadiazol-5-yl.

In accordance with yet another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing, as ring members, one oxygen atom and two nitrogen atoms. Moieties contemplated by this embodiment of the invention include those wherein A is 1,2,6-oxadiazin-3-yl, 1,2,5-oxadiazin-3-yl, 1,2,4-oxadiazin-3-yl, 1,2,5-oxadiazin-4-yl, 1,2,3-oxadiazin-4-yl, 1,3,4-oxadiazin-5-yl, 1,3,4-oxadiazin-2-yl, 1,2,4-oxadiazin-5-yl, 1,3,5-oxadiazin-4-yl, 1,3,5-oxadiazin-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,3-oxadiazol-4-yl, 1,3,4-oxadiazol-2-yl, 1,2,5-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, oxadiazepinyl, and the like. Presently preferred moieties include those wherein A is 1,2,4-oxadiazol-3-yl, 1,2,3-oxadiazol-4-yl, 1,3,4-oxadiazol-2-yl, 1,2,5-oxadiazol-3-yl and 1,2,4-oxadiazol-5-yl.

In accordance with still another embodiment of the invention, A is a 5-, 6-, or 7-membered ring containing as ring members, one up to six nitrogen atoms, and/or one up to six carbon atoms, and/or zero up to five sulfur atoms, and/or zero up to five oxygen atoms.

Further, in accordance with the present invention, L is a linking moiety which links moieties A and B. L is selected from substituted or unsubstituted alkenylene moieties, alkynylene moieties or azo moieties. Presently preferred compounds of the invention are those wherein L is alkenylene or alkynylene moieties containing two carbon atoms, with alkynylene most preferred.

Further, in accordance with the present invention, B is a moiety linked through bridging moiety L to moiety A. Radicals contemplated for use in the invention are those wherein B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, substituted or unsubstituted aryl, and the like.

Presently preferred compounds of the invention are those wherein B is a substituted or unsubstituted hydrocarbyl selected from substituted or unsubstituted alkyl moieties, alkenyl moieties, dialkenyl moieties, trialkenyl moieties, alkynyl moieties, alkadiynyl moieties, alkatriynyl moieties, alkenynyl moieties, alkadienynyl moieties, alkenediynyl moieties, and the like.

Further preferred compounds of the invention are those wherein B is a substituted or unsubstituted cyclohydrocarbyl selected from substituted or unsubstituted cycloalkyl moieties, cycloalkenyl moieties, cycloalkadienyl moieties, cycloalkatrienyl moieties, cycloalkynyl moieties, cycloalkadiynyl moieties, bicyclic hydrocarbon moieties wherein two rings have two atoms in common, and the like. Especially preferred compounds are those wherein B is cycloalkyl and cycloalkenyl having in the range of 4 up to about 8 carbon atoms. Exemplary compounds include cyclopropanyl, cyclopentenyl and cyclohexenyl. Also especially preferred are bicyclic hydrocarbon moieties wherein two rings have two atoms in common; exemplary compounds include indenyl, dihydroindenyl, naphthalenyl and dihydronaphthalenyl.

Still further preferred compounds of the invention are those wherein B is a substituted or unsubstituted heterocycle, optionally containing one or more double bonds. Exemplary compounds include pyridyl, thiazolyl, furyl, dihydropyranyl, dihydrothiopyranyl, piperidinyl, isoxazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like. Also preferred are compounds wherein B is substituted or unsubstituted aryl. Especially preferred compounds are those wherein substituents are aryl and heterocycle, optionally bearing further substituents as described herein, methyl, trifluoromethyl, cyclopropyl, alkoxy, halogen and cyano. Also preferred are compounds wherein B is a bicylic heterocyle moiety wherein two rings have two atoms in common. Exemplary compounds include indolyl and isoquinolinyl.

Those of skill in the art recognize that invention compounds may contain one or more chiral centers, and thus can exist as racemic mixtures. For many applications, it is preferred to carry out stereoselective syntheses and/or to subject the reaction product to appropriate purification steps so as to produce substantially optically pure materials. Suitable stereoselective synthetic procedures for producing optically pure materials are well known in the art, as are procedures for purifying racemic mixtures into optically pure fractions. Those of skill in the art will further recognize that invention compounds may exist in polymorphic forms wherein a compound is capable of crystallizing in different forms. Suitable methods for identifying and separating polymorphisms are known in the art.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, esterified carboxy is, for example, lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl or phenyl-lower alkoxycarbonyl substituted in the phenyl moiety by one or more substituents selected from lower alkyl, lower alkoxy, halo and halo-lower alkyl. Esterified carboxy-lower-alkoxy is, for example, lower alkoxycarbonyl-lower alkoxy. Amidated carboxy is, for example, unsubstituted or aliphatically substituted carbamoyl such as carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-phenyl- or N-lower-alkyl-N-phenyl-carbamoyl.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, acyl is, for example, lower alkanoyl, lower alkenoyl or unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted benzoyl. Acylamino is, for example, lower alkanoylamino, and N-acyl-N-lower alkylamino is, for example, N-lower alkanoyl-N-lower-alkylamino or unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted benzoylamino.

As referred to in reference to compounds excluded herein when referring to novel compounds of the invention, "lower" groups are understood to comprise up to and including seven carbon atoms. N-lower-alkyl-N-phenylcarbamoyl is, for example, N-C_1-C_4alkyl-N-phenylcarbamoyl, such as N-methyl, N-ethyl, N-propyl, N-isopropyl or N-butyl-N-phenylcarbamoyl.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, amino-lower alkyl is, for example, amino-C_1-C_4alkyl, preferably of the formula -$(CH_2)_n$-NH_2 in which n is 2 or 3, such as aminomethyl, 2-aminoethyl, 3-aminopropyl or 4-aminobutyl. Hydroxy-lower alkyl is, for example, hydroxy-C_1-C_4alkyl, such as hydroxymethyl, 2-hydroxy ethyl, 3-hydroxypropyl, 2-hydroxyisopropyl or 4-hydroxybutyl. Halo-lower alkyl is, for example, polyhalo-C_1-C_4alkyl, such as trifluoromethyl.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, lower alkoxy is, for example, C_1-C_7alkoxy, preferably C_1-C_4alkoxy, such as methoxy, ethoxy, propyloxy, isopropyloxy or butyloxy, but may also represent isobutyloxy, sec.butyloxy, tert.-butyloxy or a C_5-C_7alkoxy group, such as a pentyloxy, hexyloxy or heptyloxy group.amino-lower alkoxy is, for example, amino-C_2-C_4alkoxy preferably of the formula -O-$(CH_2)_n$-NR_aR_b in which n is 2 or 3, such as 2-aminoethoxy, 3-aminopropyloxy or 4-aminobutyloxy. Carboxy-lower-alkoxy is, for example, carboxy-C_1-C_4alkoxy, such as carboxymethoxy, 2-carboxyethoxy, 3-carboxypropyloxy or 4-carboxybutyloxy. Lower alkanoyloxy is, for example, C_1-C_7alkanoyloxy, such as acetoxy, propionyloxy, butyryloxy, isobutyryloxy or pivaloyloxy. Halo-lower alkoxy is, for example, halo- or polyhalo-C_1-C_7alkoxy, preferably halo- or polyhalo-C_1-C_4alkoxy, such as halo- or polyhaloethoxy, halo- or polyhalopropyloxy or butyl-oxy, wherein "poly" refers, for example, to tri- or pentahalo, and "halo" denotes, for example, fluoro or chloro.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, lower alkylamino-lower alkoxy is, for example, C_1-C_4alkylamino-C_2-C_4alkoxy, preferably of the formula -O-(CH_2)n-NR_aR_b in which n is 2 or 3 and R_a and R_b, independently of each other, denote lower alkyl groups as defined hereinbefore, such as methyl, ethyl, propyl or butyl. Lower alkylamino-lower alkyl is, for example, C_1-C_4alkylamino-C_1-C_4alkyl, preferably of the formula -$(CH_2)_n$-NR_aR_b in which n is 2 or 3 and R_a and R_b, independently of each other, denote lower alkyl groups as defined hereinbefore, such as methyl, ethyl, propyl or butyl. Di-lower alkylamino-lower alkyl is, for example, Di-C_1-C_4alkylamino-C_1-C_4alkyl, preferably of the formula -$(CH_2)_n$-NR_aR_b in which n is 2 or 3 and R_a and R_b, independently of each other, denote lower alkyl groups such as methyl, ethyl, propyl or butyl. Di-lower alkylamino-lower alkoxy is, for example, Di-C_1-C_4alkylamino-C_2-C_4alkoxy, preferably of the formula -O-$(CH_2)_n$-NR_aR_b in which n is 2 or 3 and R_a and R_b, independently of each other, denote lower alkyl groups such as methyl, ethyl, propyl or butyl.

As used herein, with reference to compounds excluded herein when referring to novel compounds of the invention, optionally hydroxy-substituted lower alkyleneamino-lower alkyl is, for example, unsubstituted or hydroxy-substituted 5- to 7-membered alkyleneamino-C_1-C_4alkyl, preferably of the formula -$(CH_2)_n$-R_c in which n is 2 or 3 and R_c pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, homopiperidino or hydroxyhomopiperidino. Furthermore, optionally hydroxy-

substituted lower alkyleneamino-lower alkoxy is, for example, unsubstituted or hydroxy-substituted 5- to 7-membered alkyleneamino-C_1-C_4alkoxy, preferably of the formula -O-$(CH_2)_n$-R_c in which n is 2 or 3 and R_c pyrrolidino, hydroxypyrrolidino, piperidino, hydroxypiperidino, homopiperidino or hydroxyhomopiperidino.

In accordance with another embodiment of the present invention, there are provided pharmaceutical compositions comprising heterocyclic compounds as described above, in combination with pharmaceutically acceptable carriers. Optionally, invention compounds can be converted into non-toxic acid addition salts, depending on the substituents thereon. Thus, the above-described compounds (optionally in combination with pharmaceutically acceptable carriers) can be used in the manufacture of medicaments useful for the treatment of a variety of indications.

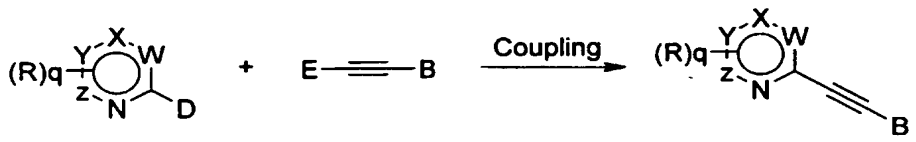
Pharmaceutically acceptable carriers contemplated for use in the practice of the present invention include carriers suitable for oral, sublingual intravenous, subcutaneous, transcutaneous, intramuscular, intracutaneous, intrathecal, epidural, intraoccular, intracranial, inhalation, rectal, vaginal, and the like administration. Administration in the form of creams, lotions, tablets, capsules, pellets, dispersible powders, granules, suppositoiries, syrups, elixirs, lozenges, injectable solutions, sterile aqueous or non-aqueous solutions, suspensions or emulsions, patches, and the like, is contemplated. Pharmaceutically acceptable carriers include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, dextrans, and the like.

Invention compounds can optionally be converted into non-toxic acid addition salts. Such salts are generally prepared by reacting the compounds of this invention with a suitable organic or inorganic acid. Representative salts include hydrochloride, hydrobromide, sulfate, bisulfate, methanesulfonate, acetate, oxalate, adipate, alginate, aspartate, valerate, oleate, laurate, borate, benzoate, lactate, phosphate, toluenesulfonate (tosylate), citrate, malate, maleate, fumarate, succinate, tartrate, napsylate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, benzenesulfonate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, glucoheptanoate, glycerophosphate, heptanoate, hexanoate, undecanoate, 2-hydroxyethanesulfonate,ethanesulfonate, and the like. Salts can also be formed with inorganic acids such as sulfate, bisulfate, hemisulfate, hydrochloride, chlorate, perchlorate, hydrobromide, hydroiodide, and the like. Examples of a base salt include ammonium salts; alkali metal salts such as sodium salts, potassium salts, and the like; alkaline earth metal salts such as calcium salts, magnesium salts, and the like; salts with organic bases such as dicyclohexylamine salts, *N*-methyl-D-glucamine, phenylethylamine, and the like; and salts with amino acids such as arginine, lysine, and the like. Such salts can readily be prepared employing methods well known in the art.

In accordance with another embodiment of the present invention, there are provided methods

for the preparation of heterocyclic compounds as described above. For example, many of the heterocyclic compounds described above can be prepared using synthetic chemistry techniques well known in the art (see *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R. and Rees, C. W. eds., Pergamon Press, Oxford, 1984) from a precursor of the substituted heterocycle of Formula 1 as outlined in Scheme 1.

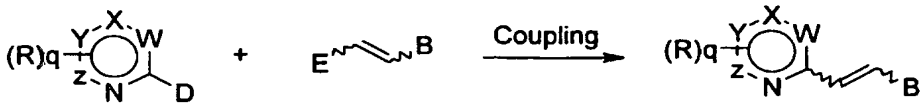
Scheme 1



Thus in Scheme 1, a substituted heterocycle precursor (prepared using synthetic chemistry techniques well known in the art) is reacted with an alkyne derivative. In Scheme 1, $(R)_q$, W, X, Y, Z and B are as defined above and D and E are functional groups which are capable of undergoing a transition metal-catalyzed cross-coupling reaction. For example, D is a group such as hydrogen, halogen, acyloxy, fluorosulfonate, trifluoromethanesulfonate, alkyl- or arylsulfonate, alkyl- or arylsulfinate, alkyl- or arylsulfide, phosphate, phosphinate, and the like, and E is hydrogen or a metallic or metalloid species such as Li, MgX (X is halogen), SnR_3, $B(OR)_2$, SiR_3, GeR_3, and the like. The coupling may be promoted by a homogeneous catalyst such as $PdCl_2(PPh_3)_2$, or by a heterogeneous catalyst such as Pd on carbon in a suitable solvent (*e.g.*, tetrahydrofuran (THF), dimethoxyethane (DME), acetonitrile, dimethylformamide (DMF), *etc.*). Typically, a co-catalyst such as copper (I) iodide and a base (*e.g.*, triethylamine, K_2CO_3 *etc.*) will also be present in the reaction mixture. The coupling reaction typically proceeds by allowing the reaction temperature to warm slowly from about 0° C up to ambient temperature over a period of several hours. The reaction mixture is then maintained at ambient temperature, or heated to a temperature anywhere between 30° C and 150° C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to 48 hours, with about 12 hours typically being sufficient. The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation, and the like.

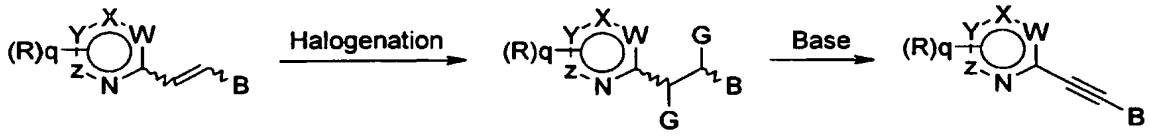
Another embodiment of the present invention is illustrated in Scheme 2. A substituted heterocycle precursor is reacted with an alkene derivative in a manner similar to the procedure described for Scheme 1.

Scheme 2



The alkene derivative product from Scheme 2 may be converted to an alkyne derivative using the approach outlined in Scheme 3.

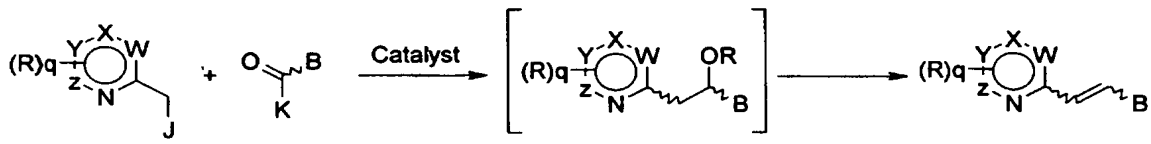
Scheme 3



Thus, the alkene derivative may be contacted with a halogenating agent such as chlorine, bromine, iodine, NCS (N-chlorosuccinimide), NBS (N-bromosuccinimide), NIS (N-iodosuccinimide), iodine monochloride, etc. in a suitable solvent (CCl_4, $CHCl_3$, CH_2Cl_2, acetic acid, and the like). The resulting halogenated derivative (G = halogen) is then treated with a suitable base such as NaOH, KOH, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DBN (diazabicyclononene), DABCO (1,4-diazabicyclo[2.2.2]octane), and the like, which promotes a double elimination reaction to afford the alkyne. The reaction is carried out in a suitable solvent such as ethanol, acetonitrile, toluene, *etc.* at an appropriate temperature, usually between about 0° C and 150° C.

In another embodiment of the present invention, a substituted heterocyclic derivative is reacted with an aldehyde or ketone to provide a substituted alkene. (See Scheme 4.)

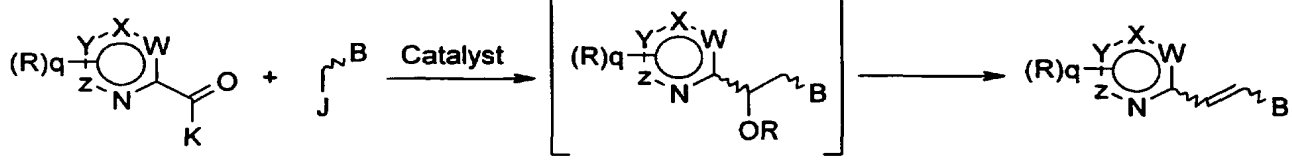
Scheme 4



Thus, in Scheme 4, J is hydrogen, PR_3, $P(O)(OR)_2$, SO_2R, SiR_3, and the like, K is hydrogen, alkyl or aryl (as defined previously) and R is hydrogen, acetyl, and the like. Suitable catalysts for this reaction include bases such as NaH, *n*-buytllithium, lithium diisopropylamide, lithium hexamethyl disilazide, H_2NR, HNR_2, NR_3 *etc.*, or electropositive reagents such as Ac_2O, $ZnCl_2$, and the like. The reaction is carried out in a suitable solvent (THF, acetonitrile, *etc.*) at an appropriate temperature, usually between about 0° C and 150° C. Sometimes an intermediate is isolated and purified or partially purified before continuing through to the alkene product.

In yet another embodiment of the present invention, a substituted heterocyclic aldehyde or ketone is reacted with an activated methylene-containing compound to provide a substituted alkene. (See Scheme 5.)

Scheme 5

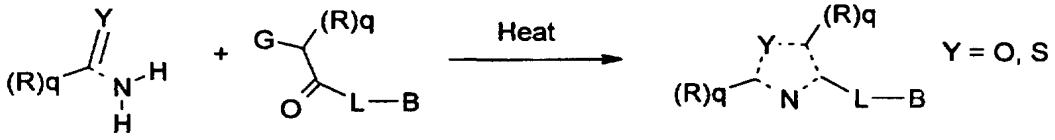


Thus, in Scheme 5, J, K, R, the catalyst and reaction conditions are as described for Scheme 4. Again, as in Scheme 4, sometimes an intermediate is isolated and purified or partially purified before continuing through to the alkene product.

The alkene products from the reactions in Scheme 4 and Scheme 5 may be converted to an alkyne derivative using reagents and conditions as described for Scheme 3.

Another method for the preparation of heterocyclic compounds of Formula I is depicted in Scheme 6.

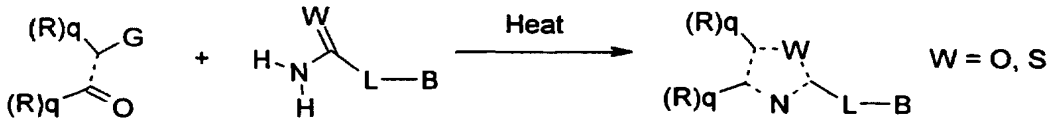
Scheme 6



In scheme 6, Y is O or S and G is halogen or a similar leaving group, and L and B are as defined previously. The reagents are contacted in a suitable solvent such as ethanol, DMF, and the like and stirred until the product forms. Typically reaction temperatures will be in the range of ambient through to about 150° C, and reaction times will be from about 1 h to about 48 h, with about 70° C and 4 h being presently preferred. The heterocycle product can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation, and the like. Often, the product will be isolated as the hydrochloride or hydrobromide salt, and this material may be carried onto the next step with or without purification.

Yet another method for the preparation of heterocyclic compounds of Formula I is depicted in Scheme 7.

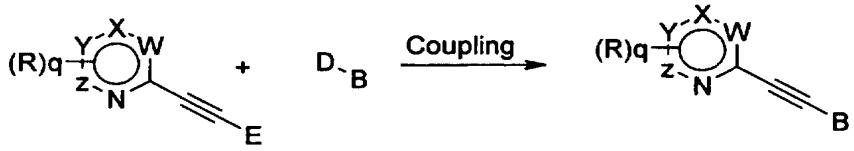
Scheme 7



In Scheme 7, W may be O or S, G is halogen or a similar leaving group, and L and B are as defined previously. The reaction conditions and purification procedures are as described for Scheme 6.

In another embodiment of the present invention, depicted in Scheme 8, an alkynyl-substituted heterocycle precursor (prepared using synthetic chemistry techniques well known in the art) is reacted with a species B, bearing a reactive functional group D (See Scheme 8.)

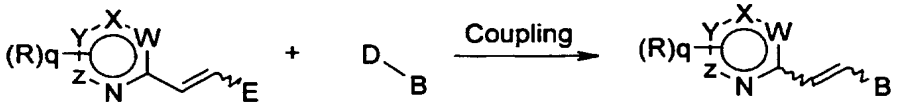
Scheme 8



In Scheme 8, $(R)_q$, W, X, Y, Z and B are as defined above and D and E are functional groups which are capable of undergoing a transition metal-catalyzed cross-coupling reaction. For example, D is a group such as hydrogen, halogen, acyloxy, fluorosulfonate, trifluoromethanesulfonate, alkyl- or arylsulfonate, alkyl- or arylsulfinate, alkyl- or arylsulfide, phosphate, phosphinate, and the like, and E is hydrogen or a metallic or metalloid species such as Li, MgX (X is halogen), SnR_3, $B(OR)_2$, SiR_3, GeR_3, and the like. The coupling may be promoted by a homogeneous catalyst such as $PdCl_2(PPh_3)_2$, or by a heterogeneous catalyst such as Pd on carbon in a suitable solvent (*e.g.* tetrahydrofuran (THF), dimethoxyethane (DME), acetonitrile, dimethylformamide (DMF), *etc.*). Typically a co-catalyst such as copper (I) iodide and the like and a base (*e.g.* triethylamine, K_2CO_3, *etc.*) will also be present in the reaction mixture. The coupling reaction is typically allowed to proceed by allowing the reaction temperature to warm slowly from about 0° C up to ambient temperature over a period of several hours. The reaction mixture is then maintained at ambient temperature, or heated to a temperature anywhere between about 30° C up to about 150° C. The reaction mixture is then maintained at a suitable temperature for a time in the range of about 4 up to about 48 hours, with about 12 hours typically being sufficient. The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation, and the like.

Another embodiment of the present invention is illustrated in Scheme 9.

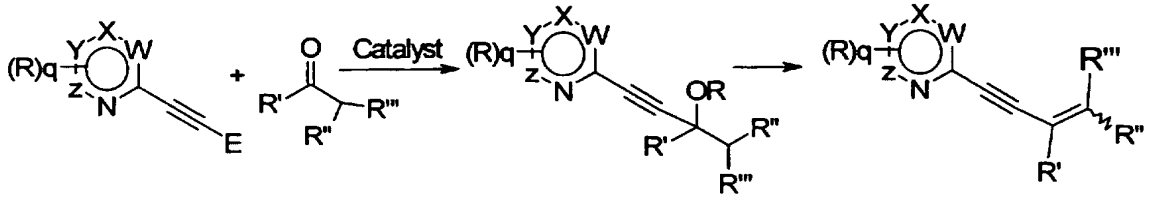
Scheme 9



An alkenyl-substituted heterocycle precursor is reacted with an alkene derivative in a manner similar to the procedure described for Scheme 8. The product alkene derivative from Scheme 9 may be converted to an alkyne derivative using the approach outlined previously in Scheme 3 above.

In yet another embodiment of the present invention, depicted in Scheme 10, an alkynyl-substituted heterocycle precursor is reacted with a species composed of a carbonyl group bearing substituents R' and CHR''R'''.

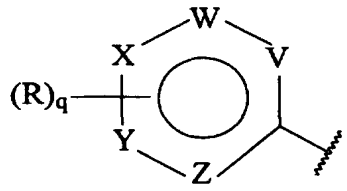
Scheme 10



Thus in Scheme 10, R', R'' and R''' may be hydrogen or other substituents as described previously, or may optionally combine to form a ring (this portion of the molecule constitutes B in the final compound). E is hydrogen or a metallic or metalloid species such as Li, MgX, wherein X is halogen, SnR_3, $B(OR)_2$, SiR_3, GeR_3, and the like. Suitable catalysts for this reaction include bases such as NaH, *n*-butyllithium, lithium diisopropylamide, lithium hexamethylsilazide, H_2NR, HNR_2, NR_3, nBu_4NF, ethylmagnesium halide, *etc.* R in Scheme 10 may be hydrogen, Ac, and the like. Typically the reaction is carried out in a suitable solvent such as diethylether, THF, DME, toluene, and the like, and at an appropriate temperature, usually between –100° C and 25° C. The reaction is allowed to proceed for an appropriate length of time, usually from about 15 minutes to about 24 hours. The intermediate bearing the -OR group may be isolated and purified as described above, partially purified or carried on to the next step without purification. Elimination of the –OR group to provide the alkene derivative may be accomplished using a variety of methods well known to those skilled in the art. For example, the intermediate may be contacted with $POCl_3$ in a solvent such as pyridine and stirred at a suitable temperature, typically between about 0° C and about 150° C, for an appropriate amount of time, usually between about 1 h and about 48 h. The product from the reaction can be isolated and purified employing standard techniques, such as solvent extraction, chromatography, crystallization, distillation, and the like.

In accordance with another embodiment of the present invention, there are provided methods of modulating the activity of excitatory amino acid receptors, said method comprising contacting said receptors with at least one compound as described above, as well as additional compounds of the same basic structure but having substitution patterns which may have been previously disclosed but never contmplated for use for such purposes. Thus, compounds contemplated for use in accordance with invention modulations methods include those having the structure **A —L— B** or enantiomers, diastereomeric isomers or mixtures of any two or more thereof, or pharmaceutically acceptable salts thereof, in an amount sufficient to modulate the activity of said excitatory amino acid receptor, wherein:

A is a 5-, 6- or 7-membered ring having the structure:



wherein at least one of **V, W, X, Y** and **Z** is $(CR)_p$, wherein p is 0, 1 or 2;

at least one of **V, W, X, Y** and **Z** is O, N or S;

the remainder of **V, W, X, Y** and **Z** are each independently O, N or S; and

each **R** is independently halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, heterocycle, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxy, ester, cyano, amine, amide, amidine, amido, sulfonyl or sulfonamide, wherein q is 0, 1, 2 or 3;

L is substituted or unsubstituted alkenylene, alkynylene, or azo; and

B is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocycle, optionally containing one or more double bonds, or substituted or unsubstituted aryl;

provided, that the following compounds are excluded:

the compounds wherein A is a 6-membered ring wherein:

V, W, X and **Y** are (CR)p, wherein p is 1,

Z is N;

R at the V position is hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, unsubstituted or hydroxy-substituted lower alkyleneamino-lower alkyl, lower alkoxy, lower alkanoyloxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, phthalimido-lower alkoxy, unsubstituted or hydroxy- or 2-oxo-imidazolidin-1-yl-substitued lower alkyleneamino-lower alkoxy, carboxy, esterified or amidated carboxy, carboxy-lower alkoxy or esterified carboxy-lower-alkoxy; R at

the W position is hydrogen; R at the X position is hydrogen, lower alkyl, carboxy, esterified carboxy, amidated carboxy, hydroxy-lower alkyl, hydroxy, lower alkoxy or lower alkanoyloxy; and R at the Y position is hydrogen, lower alkyl, hydroxy-lower alkyl, carboxy, esterified carboxy, amidated carboxy, unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or trifluoromethyl-substituted N-lower alkyl-N-phenylcarbamoyl, lower alkoxy, halo-lower alkyl or halo-lower alkoxy;

L is substituted or unsubstituted alkenylene, alkynylene or azo, and

B is substituted or unsubstituted aryl or heterocycle having two or more double bonds, wherein substituents are independently lower alkyl, lower alkenyl, lower alkynyl, phenyl, phenyl-lower alkynyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkanoyloxy, phenoxy, phenyl-lower alkoxy, acyl, carboxy, esterified carboxy, amidated carboxy, cyano, nitro, amino, acylamino, N-acyl-N-lower alkylamino, halo and halo-lower alkyl, wherein phenyl, phenyl-lower alkynyl, phenoxy, and phenyl-lower alkoxy may bear further substituents.

As employed herein, "excitatory amino acid receptors" refers to a class of cell-surface receptors which are the major class of excitatory neurotransmitter receptors in the central nervous system. In addition, receptors of this class also mediate inhibitory responses. Excitatory amino acid receptors are membrane spanning proteins that mediate the stimulatory actions of the amino acid glutamate and possibly other endogenous acidic amino acids. Excitatory amino acids are crucial for fast and slow neurotransmission and they have been implicated in a variety of diseases including Alzheimer's disease, stroke, schizophrenia, head trauma, epilepsy, and the like. In addition, excitatory amino acids are integral to the processes of long-term potentiation and depression which are synaptic mechanisms underlying learning and memory. There are three main subtypes of excitatory amino acid receptors: (1) the metabotropic receptors; (2) the ionotropic NMDA receptors; and (3) the non-NMDA receptors, which include the AMPA receptors and kainate receptors.

As employed herein, the phrase "modulating the activity of" refers to altered levels of activity so that the activity is different with the use of the invention method when compared to the activity without the use of the invention method. Modulating the activity of excitatory amino acid receptors includes the suppression or augmentation of the activity of receptors. Suppression of receptor activity may be accomplished by a variety of means, including blocking of a ligand binding site, biochemical and/or physico-chemical modification of a ligand binding site, binding of agonist recognition domains, preventing ligand-activated conformational changes in the receptor, preventing the activated receptor from stimulating second messengers such as G-proteins, and the like. Augmentation of receptor activity may be accomplished by a variety of means including, stabilization of a ligand binding site, biochemical and/or physico-chemical modification of a ligand binding site, binding of agonist recognition domains, promoting ligand-activated conformational changes in the receptor, and the like.

Excitatory amino acid receptor activity can be involved in numerous disease states. Therefore modulating the activity of receptors also refers to a variety of therapeutic applications, such as the treatment of cerebral ischemia, chronic neurodegeneration, psychiatric disorders, schizophrenia, mood disorders, emotion disorders, disorders of extrapyramidal motor function, obesity, disorders of respiration, motor control and function, attention deficit disorders, concentration disorders, pain disorders, neurodegenerative disorders, epilepsy, convulsive disorders, eating disorders, sleep disorders, sexual disorders, circadian disorders, drug withdrawal, drug addiction, compulsive disorders, anxiety, panic disorders, depressive disorders, skin disorders, retinal ischemia, retinal degeneration, glaucoma, disorders associated with organ transplantation, asthma, ischemia or astroytomas, and the like.

The compounds contemplated for use in accordance with of invention modulatory methods are especially useful for the treatment of mood disorders such as anxiety, depression, psychosis, drug withdrawal, tobacco withdrawal, memory loss, cognitive impairment, dementia, Alzheimer's disease, and the like; disorders of extrapyramidal motor function such as Parkinson's disease, progressive supramuscular palsy, Huntington's disease, Gilles de la Tourette syndrome, tardive dyskinesia, and the like.

Compounds contemplated for use in accordance with invention modulatory methods are also especially useful for the treatment of pain disorders such as neuropathic pain, chronic pain, acute pain, painful diabetic neuropathy, post-herpetic neuralgia, cancer-associated pain, pain associated with chemotherapy, pain associated with spinal cord injury, pain associated with multiple sclerosis, causalgia and reflex sympathetic dystrophy, phantom pain, post-stroke (central) pain, pain associated with HIV or AIDS, trigeminal neuralgia, lower back pain, myofacial disorders, migraine, osteoarthritic pain, postoperative pain, dental pain, post-burn pain, pain associated with systemic lupus, entrapment neuropathies, painful polyneuropathies, ocular pain, pain associated with inflammation, pain due to tissue injury, and the like.

"Contacting" may include contacting in solution or in solid phase.

"Pharmaceutically acceptable salt" refers to a salt of the compound used for treatment which possesses the desired pharmacological activity and which is physiologically suitable. The salt can be formed with organic acids such as acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, heptanoate, hexanoate, 2-hydroxyethanesulfonate, lactate, malate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, tartrate, toluenesulfonate, undecanoate, and the like. The salt can also be formed with inorganic acids such as sulfate, bisulfate, chlorate, perchlorate, hemisulfate, hydrochloride, hydrobromide, hydroiodide, and the like. In addition, the salt can be formed with a base salt, including

ammonium salts, alkali metal salts such as sodium salts, potassium salts, and the like; alkaline earth metal salts such as calcium salts, magnesium salts, and the like; salts with organic bases such as dicyclohexylamine salts, *N*-methyl-D-glucamine, phenylethylamine, and the like; and salts with amino acids such as arginine, lysine, and the like.

Salt forms of compounds herein find several advantages. Certain pharmaceutically acceptable salt forms of heterocyclic compounds described herein, achieve higher solubility as compared with non-salt forms. In addition, certain salt forms are more compatible with pharmaceutical uses. For example, the hydrochloric acid salt of 2-(phenylethynl)-1,3-thiazole is an oil while the toluene sulfonic acid salt form of 2-(phenylethynl)-1,3-thiazole is a solid that is soluble in aqueous medium. (See Example 187.) Characteristics of salt forms of compounds depend on the characteristics of the compound so treated, and on the particular salt employed.

In accordance with another embodiment of the invention, there are provided methods of modulating the activity of metabotropic glutamate receptors, said method comprising contacting metabotropic glutamate receptors with a concentration of a heterocylic compound as described above in accordance with invention methods for modulating the acitivity of excitatory amino acid receptors, sufficient to modulate the activity of said metabotropic glutamate receptors.

As used herein, the phrase "metabotropic glutamate receptor" refers to a class of cell-surface receptors which participates in the G-protein-coupled response of cells to glutamatergic ligands. Three groups of metabotropic glutamate receptors, identified on the basis of amino acid sequence homology, transduction mechanism and binding selectivity are presently known and each group contains one or more types of receptors. For example, Group I includes metabotropic glutamate receptors 1 and 5 (mGluR1 and mGluR5), Group II includes metabotropic glutamate receptors 2 and 3 (mGluR2 and mGluR3) and Group III includes metabotropic glutamate receptors 4, 6, 7 and 8 (mGluR4, mGluR6, mGluR7 and mGluR8). Several subtypes of each mGluR type may be found; for example, subtypes of mGluR1 include mGluR1a, mGluR1b and mGluR1c.

In accordance with another embodiment of the invention, there are provided methods of treating a wide variety of disease conditions, said method comprising administering to a patient having a disease condition a therapeutically effective amount of at least one of the heterocyclic compounds described above in accordance with invention methods for modulating the activity of excitatory amino acid receptors.

As used herein, "treating" refers to inhibiting or arresting the development of a disease, disorder or condition and/or causing the reduction, remission, or regression of a disease, disorder or condition. Those of skill in the art will understand that various methodologies and assays may be used to assess the development of a disease, disorder or condition, and similarly, various methodologies and assays may be used to assess the reduction, remission or regression of a disease, disorder or condition.

Disease conditions contemplated for treatment in accordance with the invention include cerebral ischemia, chronic neurodegeneration, psychiatric disorders, schizophrenia, mood disorders, emotion disorders, disorders of extrapyramidal motor function, obesity, disorders of respiration, motor control and function, attention deficit disorders, concentration disorders, pain disorders, neurodegenerative disorders, epilepsy, convulsive disorders, eating disorders, sleep disorders, sexual disorders, circadian disorders, drug withdrawal, drug addiction, compulsive disorders, anxiety, panic disorders, depressive disorders, skin disorders, retinal ischemia, retinal degeneration, glaucoma, disorders associated with organ transplantation, asthma, ischemia, astrocytomas, and the like.

Disease conditions contemplated for treatment in accordance with the present invention further include diseases of the pulmonary system, diseases of the nervous system, diseases of the cardiovascular system, diseases of the gastrointestinal system, diseases of the endocrine system, diseases of the exocrine system, diseases of the skin, cancer, diseases of the ophthalmic system, and the like.

As used herein, "administering" refers to means for providing heterocyclic compounds and/or salts thereof, as described herein, to a patient, using oral, sublingual intravenous, subcutaneous, transcutaneous, intramuscular, intracutaneous, intrathecal, epidural, intraoccular, intracranial, inhalation, rectal, vaginal, and the like administration. Administration in the form of creams, lotions, tablets, capsules, pellets, dispersible powders, granules, suppositoiries, syrups, elixirs, lozenges, injectable solutions, sterile aqueous or non-aqueous solutions, suspensions or emulsions, patches, and the like, is also contemplated. The active ingredients may be compounded with non-toxic, pharmaceutically acceptable carriers including, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, dextrans, and the like.

For purposes of oral administration, tablets, capsules, troches, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, elixirs and lozenges containing various excipients such as calcium carbonae, lactose, calcium phosphate, sodium phosphate, and the like may be employed along with various granulating and disintegrating agents such as corn starch, potato starch, alginic acid, and the like, together with binding agents such as gum tragacanth, corn starch, gelatin, acacia, and the like. Lubricating agents such as magnesium stearate, stearic acid, talc, and the like may also be added. Preparations intended for oral use may be prepared according to any methods known to the art for the manufacture of pharmaceutical preparations and such preparations may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, saccharin, and the lake, flavoring agents such as peppermint, oil of wintergreen, and the like, coloring agents and preserving agents in order to provide pharmaceutically palatable preparations. Preparations for oral use may also contain suitable carriers include emulsions, solutions, suspensions, syrups, and the like, optionally containing additives such as wetting agents, emulsifying and suspending

agents, sweetening, flavoring and perfuming agents, and the like. Tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period of time.

For the preparation of fluids for parenteral administration, suitable carriers include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. For parenteral administration, solutions for the practice of the invention may comprise sterile aqueous saline solutions, or the corresponding water soluble pharmaceutically acceptable metal salts, as previously described. For parenteral administration, solutions of the compounds used in the practice of the invention may also comprise non-aqueous solutions, suspensions, emulsions, and the like. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile water, or some other sterile injectable medium immediately before use.

Aqueous solutions may also be suitable for intravenous, intramuscular, intrathecal, subcutaneous, and intraperitoneal injection. The sterile aqueous media employed are all readily obtainable by standard techniques well known to those skilled in the art. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, by heating the compositions, and the like. They can also be manufactured in the form of sterile water, or some other sterile medium capable of injection immediately before use.

Compounds contemplated for use in accordance with the present invention may also be administered in the form of suppositories for rectal or vaginal administration. These compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, and the like, such materials being solid at ambient temperatures but liquify and/or dissolve in internal cavities to release the drug.

The preferred therapeutic compositions for inocula and dosage will vary with the clinical indication. Some variation in dosage will necessarily occur depending upon the condition of the patient being treated, and the physician will, in any event, determine the appropriate dose for the individual patient. The effective amount of compound per unit dose depends, among other things, on the body weight, physiology, and chosen inoculation regimen. A unit dose of compound refers to the weight of compound without the weight of carrier (when carrier is used).

The route of delivery of compounds and compositions used for the practice of the invention is determined by the disease and the site where treatment is required. Since the pharmacokinetics and pharmacodynamics of compounds and compositions described herein will vary somewhat, the most preferred method for achieving a therapeutic concentration in a tissue is to gradually escalate the dosage and monitor the clinical effects. The initial dose, for such an escalating dosage regimen of therapy, will depend upon the route of administration.

In accordance with invention methods, the medicinal preparation can be introduced parenterally, by dermal application, and the like, in any medicinal form or composition. It is used as a solitary agent of medication or in combination with other medicinal preparations. Single and multiple therapeutic dosage regimens may prove useful in therapeutic protocols.

As employed herein, the phrase "a therapeutically effective amount", when used in reference to invention methods employing heterocyclic compounds and pharmaceutically acceptable salts thereof, refers to a dose of compound sufficient to provide circulating concentrations high enough to impart a beneficial effect on the recipient thereof. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated, the severity of the disorder, the activity of the specific compound used, the route of administration, the rate of clearance of the specific compound, the duration of treatment, the drugs used in combination or coincident with the specific compound, the age, body weight, sex, diet and general health of the patient, and like factors well known in the medical arts and sciences. Dosage levels typically fall in the range of about 0.001 up to 100 mg/kg/day; with levels in the range of about 0.05 up to 10 mg/kg/day being preferred.

In still another embodiment of the invention, there are provided methods for preventing disease conditions in a subject at risk thereof, said method comprising administering to said subject a therapeutically effective amount of at least one of the heterocyclic compounds described above in accordance with invention methods for modulating the activity of excitatory amino acid receptors.

As used herein, the phrase "preventing disease conditions" refers to preventing a disease, disorder or condition from occurring in a subject who may be at risk for the disease, but has not yet been diagnosed as having the disease. Those of skill in the art will understand that a variety of methods may be used to determine a subject at risk for a disease, and that whether a subject is at risk for a disease will depend on a variety of factors known to those of skill in the art, including genetic make-up of the subject, age, body weight, sex, diet, general health, occupation, exposure to environmental conditions, marital status, and the like, of the subject.

Those of skill in the art can readily identify a variety of assays that can be used to assess the activity of excitatory amino acid receptors. For receptor species that activate a second messenger

pathway, assays that measure receptor-activated changes in intracellular second messengers can be employed to monitor receptor activity. For example, inhibition of G-protein-coupled metabotropic glutamate receptors by antagonists can lead to inhibition of the glutamate-evoked increase in phosphatidylinositol (PI) hydrolysis, which can be assessed by measuring decreases in glutamate-stimulated products of PI hydrolysis. (See *e.g.*, Berridge *et al,* (1982) *Biochem. J.* 206:587-5950; and Nakajima *et al., J. Biol. Chem.* 267:2437-2442 (1992) and Example 23.) Similarly, activation of excitatory amino acid receptors that leads to the release of intracellular calcium or changes in intracellular calcium concentration can also be used to assess excitatory amino acid receptor activity. Methods of detection of transient increases in intracellular calcium concentration are well known in the art. (See *e.g.*, Ito *et al., J. Neurochem.* 56:531-540 (1991) and Example 22). Furthermore, for receptor species that mediate analgesia, assays that measure analgesic efficacy can be employed to monitor receptor activity (See Example 24).

The following examples are intended to illustrate but not to limit the invention in any manner, shape, or form, either explicitly or implicitly. While they are typical of those that might be used, other procedures, methodologies, or techniques known to those skill in the art may alternatively be used.

Example 1

Synthesis of 2-(1-Cyclohexen-1-ylethynyl)-1,3-thiazole

Triphenylphosphine (570 mg, 2.0 mmol) was dissolved in tetrahydrofuran (THF) (20 mL), then argon was bubbled through the solution for several minutes to deoxygenate it. Palladium(II) acetate (120 mg, 0.54 mmol) was added, and the reaction mixture was heated to 60°C for 0.5 h, and then cooled to ambient temperature. CuI (308 mg, 1.6 mmol), 2-bromo-1,3-thiazole (3.0 g, 18 mmol), 1-ethynylcyclohexene (2.4 g, 20 mmol), potassium carbonate (6 g, 45 mmol) and water (1.0 mL, 58 mmol) were dissolved in 50 mL dimethoxyether (DME) and argon was bubbled through the solution for several minutes to deoxygenate the mixture. The catalyst solution of triphenylphosphine and palladium (II) acetate in THF was added to the reaction flask which was heated to 75°C for 2h. After 2 h, heating was discontinued and the reaction was allowed to cool to ambient temperature. After stirring for 16 h, gas chromatography/mass spectrometry (GC/MS) analysis showed the reaction to be complete. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL) and washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 97:3 hexane:ethyl acetate to afford 2-(1-cyclohexen-1-ylethynyl)-1,3-thiazole (2.56 g, 74% yield) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, J=3.0 Hz, 1H), 7.31 (d, J=3.0 Hz, 1H), 6.37-6.35 (m, 1H), 2.23-2.14 (m, 4H), 1.71-1.57 (m, 4H). MS (ESI) 190.0 (M^++H).

Example 2

Synthesis of 2-Methyl-4-(1,3-thiazol-2-yl)-3-butyn-2-ol

2-Bromo-1,3-thiazole (6.0 g, 37 mmol) and CuI (1.3 g, 7.3 mmol) were combined in DME (150 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (25 mL, 180 mmol) and $PdCl_2(PPh_3)_2$ (2.5 g, 3.7 mmol) were added and 2-methyl-3-butyne-2-ol (4.6 g, 55 mmol) was added dropwise. After stirring at ambient temperature for 16 h, GC/MS showed the reaction was not complete. The reaction was heated to reflux for 2 h. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (600 mL), washed with water (600 mL), brine (600 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 7:3 hexane:ethyl acetate to afford 4-(2-thiazolyl)-2-methyl-3-butyn-2-ol contaminated with 2,7-dimethyl-but-3,5-diyne-2,7-diol (the dimer of 2-methyl-3-butyne-2-ol). The product was crystallized from boiling hexane to afford 2-methyl-4-(1,3-thiazol-2-yl)-3-butyn-2-ol (2.18 g, 36% yield) as off white crystals that were contaminated with a small amount of 2,7-dimethyl-but-3,5-diyne-2,7-diol. M.p. 69-70°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J=3.0 Hz, 1H), 7.34 (d, J=3.0 Hz, 1H), 4.40 (s, 1H), 1.65 (s, 6H). MS (ESI) 168.1 (M^++H).

Example 3

Synthesis of 5-Chloro-3-pyridinyl trifluoromethanesulfonate

Trifluoromethanesulfonic anhydride (5.0 mL, 30 mmol) was dissolved in CH_2Cl_2 (100 mL), and cooled to 0°C 5-Chloro-3-pyridinol (3.10 g, 23.9 mmol), and triethylamine (6.5 mL, 47 mmol) were dissolved in CH_2Cl_2 (50 mL), and the resulting solution was added to the cold trifluoromethanesulfonic anhydride solution dropwise via cannula. The resulting dark brownish-red solution was stirred at 0°C for 5 minutes, and then the ice bath was removed and the reaction mixture was allowed to warm to ambient temperature. After stirring for 16 h at ambient temperature the reaction was quenched by pouring into water and basified by addition of saturated aqueous sodium carbonate. The basic aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL), the combined organics were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting black viscous oil was filtered through a plug of silica gel and fractions were collected while eluting with 1:1 hexane:ethyl acetate. Fractions containing the desired product were combined, concentrated *in vacuo*, and further purified by column chromatography eluting with 15:1 then 10:1 hexane:ethyl acetate to afford 5-chloro-3-pyridinyl trifluoromethanesulfonate (3.68 g, 59% yield) as a golden liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65 (d, J=2 Hz, 1H), 8.52 (d, J=2 Hz, 1H), 7.70 (t, J=3 Hz, 1H). MS (ESI) 261 (M^+, ^{35}Cl), 263 (M^+, ^{37}Cl).

Example 4

Synthesis of 3-Chloro-5-[(trimethylsilyl)ethynyl]pyridine

5-Chloro-3-pyridinyl trifluoromethanesulfonate (4.0 g, 15 mmol) and CuI (580 mg, 3.0 mmol) were combined in DME (100 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (10.6 mL, 76.5 mmol), and $PdCl_2(PPh_3)_2$ (1.1g, 1.5 mmol) were added, then trimethylsilyl-acetylene (3.3 ml, 23 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 1 h at which time GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 99:1 hexane:ethyl acetate to afford 3-chloro-5-[(trimethylsilyl)ethynyl]pyridine (2.8 g, 87% yield) as a brown solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.51 (s, 1H), 8.44 (s, 1H), 7.70(s, 1H), 0.22 (s, 9H). MS (EI ionization) 209 (M^+).

Example 5

Synthesis of 3-Chloro-5-ethynylpyridine

3-Chloro-5-[(trimethylsilyl)ethynyl]pyridine (1.4g, 6.7mmol) was dissolved in methanol (15 ml) and cooled to 0°C, to the resulting solution was added potassium carbonate (93 mg, 0.67 mmol). The ice bath was removed and the reaction mixture was stirred at ambient temperature for 0.5 h at which time thin layer chromatography (TLC) and GC/MS analysis indicated that the reaction was complete. The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether (50 mL), washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 3-chloro-5-ethynylpyridine (822mg, 90% yield) which was pure by GC/MS analysis. MS (EI ionization) 137 (^{35}Cl M^+), 139 (^{37}Cl M^+). This material was carried on to the next step without further purification.

Example 6

Synthesis of 3-Chloro-5-(1,3-thiazol-2-ylethynyl)pyridine

2-Bromo-1,3-thiazole (980 mg, 6.0 mmol) and CuI (230 mg, 1.2 mmol) were combined in DME (15 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (4.2 mL, 30 mmol) and $PdCl_2(PPh_3)_2$ (420 mg, 0.60 mmol) were added, then 3-chloro-5-ethynylpyridine (820 mg, 19 mmol) was added dropwise. After stirring at ambient temperature for 16 h, GC/MS analysis showed starting material remaining. The reaction mixture was heated at reflux for 2 h. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was

dissolved in ethyl acetate (100 mL), and washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 9:1 hexane:ethyl acetate to afford 3-chloro-5-(1,3-thiazol-2-ylethynyl)pyridine which contained some dimer. This material was crystallized from hot ethyl acetate to afford 3-chloro-5-(1,3-thiazol-2-ylethynyl)pyridine (300 mg 23% yield) as light orange crystals M.p. 124-125°C. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.70 (d, J=1.5 Hz, 1H), 8.59 (d, J=3.0 Hz, 1H), 7.93 (d, J=3.0 Hz, 1H), 7.88 (t, J=2.0 Hz, 1H), 7.48 (d, J=3.0 Hz, 2H). MS (ESI) 221.1 (M^++H).

Example 7

Synthesis of 2-(Cyclohexylethynyl)-1,3-thiazole

2-Bromo-1,3-thiazole (3.1 g, 19 mmol) and CuI (290 mg, 1.5 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (13 mL, 95 mmol) and $PdCl_2(PPh_3)_2$ (530 mg, 0.76 mmol) were added and cyclohexylethyne (2.0 g, 19 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 16 h at which time GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane then 99:1 hexane:ethyl acetate to afford 2-(cyclohexylethynyl)-1,3-thiazole (1.6 g, 44% yield) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, J=9.0 Hz, 1H), 7.28 (d, J=3.0 Hz, 1H), 2.68-2.59 (m, 1H), 1.91-1.28 (m, 10H). MS (ESI) 191.7 (M^+).

Example 8

Synthesis of 2-(1-Pentynyl)-1,3-thiazole

2-Bromo-1,3-thiazole (2.0 g, 12 mmol) and CuI (183 mg, 0.96 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (8 mL, 60 mmol) and $PdCl_2(PPh_3)_2$ (337 mg, 0.48 mmol) were added and 1-pentyne (979 mg, 14.4 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 6 h at which time GC/MS analysis indicated that the reaction was not complete. Additional 1-pentyne (3.0 mL, 29 mmol) was added and the reaction was heated to 35°C under a condenser. After heating for 16 h, GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, 99:1, then 97:3 hexane:ethyl

acetate to 2-(1-pentynyl)-1,3-thiazole (820 mg, 44% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, J=3.0 Hz, 1H), 7.28 (d, J=3.0 Hz, 1H), 2.47-2.42 (m, 2H), 1.68-1.60 (m, 2H), 1.08 - 0.99 (m, 3H). MS (ESI) 151.6 (M^+).

Example 9

Synthesis of 2-(3-Cyclohexyl-1-propynyl)-1,3-thiazole

2-Bromo-1,3-thiazole (2.0 g, 12 mmol) and CuI (185 mg, 0.97 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (8.5 mL, 61 mmol) and $PdCl_2(PPh_3)_2$ (340 mg, 0.49 mmol) were added and 3-cyclohexyl-1- propyne (2.9 g, 24 mmol) was added dropwise. The reaction was stirred at ambient temperature for 16 h at which time GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, then 98:2 hexane:ethyl acetate to afford 2-(3-cyclohexyl-1-propynyl)-1,3-thiazole (1.14 g, 46% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, J=3.0 Hz, 1H), 7.27 (d, J=3.0 Hz, 1H), 2.35 (d, J=6 Hz, 2H), 1.89-1.61 (m, 5H), 1.3 - 1.03 (m, 6H). MS (ESI) 205.9 (M^++H).

Example 10

Synthesis of 2-(1-Cyclohexen-1-ylethynyl)-5-nitro-1,3-thiazole

2-Bromo-5-nitro-1,3-thiazole (2.5 g, 12 mmol) and CuI (460 mg, 2.5 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (8.4 mL, 60 mmol) and $PdCl_2(PPh_3)_2$ (840 mg, 1.2 mmol) were added and 1-ethynycyclohexene (1.5 g, 14.4 mmol) was added dropwise. The reaction was heated under reflux for 16 h at which time GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, 99:1 then 98.5:1.5 hexane:ethyl acetate to afford 2-(1-cyclohexen-1-ylethynyl)-5-nitro-1,3-thiazole (1.4 g, 51.8% yield) as a yellow powder. M.p. 85-86°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.5 (s, 1H), 6.52 (br s, 1H), 2.24 (br s, 4H), 1.63 (br s, 4H). MS (ESI) 235.1 (M^++H).

Example 11

Synthesis of 2-(3,3-Dimethyl-1-butynyl)-1,3-thiazole

Triphenylphosphine (380 mg, 1.5 mmol) was dissolved in THF (20 mL), then argon was bubbled through the solution for several minutes to deoxygenate it. Palladium(II) acetate (82 mg, 0.37 mmol) was added, and the reaction mixture was heated to 60°C for 0.5 h, and then cooled to ambient temperature. CuI (210 mg, 1.1 mmol), 2-bromo-1,3-thiazole (1.6 g, 9.8 mmol), potassium carbonate (4.2 g, 31 mmol) and water (0.70 mL, 39 mmol) were dissolved in DME (30 mL) and argon was bubbled through the mixture for several minutes to deoxygenate the mixture. 3,3-dimethyl-1-butyne (1.0 g, 12.2 mmol) was then added to mixture. The catalyst solution of triphenylphosphine and palladium (II) acetate in THF was added to the reaction flask which was heated to 30°C for 2h. After this time heating was discontinued and the mixture was allowed to stir at ambient temperature. After stirring for 16 h, GC/MS analysis showed the reaction to be complete. The mixture was filtered through Celite™, the filter pad was washed thoroughly with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), washed with water (200 mL), brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, then 99:1 hexane:ethyl acetate to afford 2-(3,3-dimethyl-1-butynyl)-1,3-thiazole (0.45 g, 28% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, J=3.0 Hz, 1H), 7.28 (d, J=3.0 Hz, 1H), 1.33 (s, 9H). MS (ESI) 166.1 (M^++H).

Example 12

Synthesis of 1-(1,3-Thiazol-2-ylethynyl)cyclopentanol

2-Bromo-1,3-thiazole (3.1 g, 19 mmol) and CuI (360 mg, 1.9 mmol) were combined in DME (30 mL) and argon gas was bubbled through the suspension for several minutes to deoxygenate the mixture. Triethylamine (13 mL, 94 mmol) and $PdCl_2(PPh_3)_2$ (660 mg, 0.94 mmol) were added and 1-ethynycyclopentanol (2.5 g, 23 mmol) was added dropwise. The reaction was heated at 50°C for 16 h at which time GC/MS analysis indicated that the reaction was complete. The mixture was filtered through Celite™, and the filter pad was washed thoroughly with ethyl acetate. The combined filtrates were concentrated *in vacuo* and the residue was dissolved in ethyl acetate (300 mL), washed with water (300 mL), brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane, 6:1 then 3:1 hexane:ethyl acetate to afford 1-(1,3-thiazol-2-ylethynyl)cyclopentanol (2.3 g, 52% yield) as a yellow powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J=3 Hz, 1H), 7.65 (d, J=3 Hz, 1H), 2.04-1.73 (m, 10.8H). MS (EI ionization) 193 (M^+).